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Please find below and/or attached an Office communication concerning this application or proceeding.

File Copy

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/545,772 | WILKINS ET AL. | |
| | Examiner | Art Unit | |
| | Vanessa L. Ford | 1645 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *10 April 2000* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-39 and 61* is/are pending in the application.

4a) Of the above claim(s) *61* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claims _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved.

12)☐ The oath or declaration is objected to by the Examiner.

**Priority under 35 U.S.C. § 119**

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

**Attachment(s)**

15) ☒ Notice of References Cited (PTO-892)
16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) ____ .
18) ☒ Interview Summary (PTO-413) Paper No(s). 12
19) ☐ Notice of Informal Patent Application (PTO-152)
20) ☐ Other:

## *DETAILED ACTION*

1. Applicant's election of Group I in Paper No. 9, filed on August 24, 2001 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). Claims 40-60 have been cancelled. Claim 61 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse.

### *Claim Objections*

2. The claims are objected to because of the following informalities: Claims 7 and 8 contain what appear to be typographical errors: Claim 7 recites "immonogenic" which should be changed to "immunogenic" and claim 8 recites "composistion" which should be changed to "composition". The Applicant is asked to review the claims for typographical errors and correction is required.

### *Claim Rejections - 35 USC § 102*

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

4. Claims 1-19 and 36-39 are rejected under 35 U.S.C. 102(b) as anticipated by Kink et al *(U.S. Patent No. 5,736,139, published April 7, 1998)*.

Claims 1-19 and 36-39 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component wherein said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized.

Kink et al disclose an immunogenic composition comprising *C. difficile* toxin A and *C. difficile* toxin fusion B proteins. Kink et al also disclose that the *C. difficile* toxin A and toxin B fusion proteins can be used to create a therapeutic vaccine (column 17, lines 51-65). Kink et al disclose that the therapeutic vaccine can be administered to a bird or a mammal (column 17, lines 65-67 and column 18, lines 1-2). Kink et al disclose that recombinant toxin proteins have been developed in a host cell of *E. coli*. In either a soluble or insoluble form (column 27, lines 12-28). Kink et al disclose that the recombinant toxin proteins produced in gram-negative bacteria (i.e. *E. coli*) can be used as vaccines. Kink et al disclose that the recombinant toxin proteins are administered to a host in any number or pharmaceutically acceptable carriers known in the art. Kink et al disclose that the recombinant toxin vaccines can be administered alone or with known adjuvants including potassium alum, aluminum phosphate, aluminum hydroxide,

Gerbu adjuvant, RIBI adjuvant or QS21adjuvant (column 27, lines 37-54). Kink et al further disclose that hamsters were vaccinated with the *C. difficile* vaccine and humoral and mucosal responses were detected by ELISA (column 153-159). It would be inherent that the therapeutic vaccine of Kink et al would comprise toxin A and toxin B repeating units or fragments thereof.

Since the Office does not have the facilities for examining and comparing applicant's immunogenic composition comprising *Clostrium difficile* toxin proteins with the immunogenic composition comprising *Clostrium difficile* toxin proteins of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the immunogenic composition of the prior art does not possess the same material structural and functional characteristics of the claimed immunogenic composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

5. Claims 1-19, and 36-39 are rejected under 35 U.S.C. 102(e) as anticipated by Thomas, Jr. et al *(U.S. Patent No. 5,919,463, filed October 16, 1995).*

Claims 1-19 and 36-39 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component wherein said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized.

Thomas, Jr. et al disclose a composition that contains an antigen, a toxin (*Clostridum difficile, C. novyi, C. sordellii, C. perfringens, C. tetani and C. botulinum*) or

a fragment or derivative thereof having adjuvant activity in a pharmaceutically acceptable vehicle (i.e. water, a saline solution, phosphate-buffered saline, a bicarbonate solution or a form of a suppository). Thomas, Jr. et al disclose that toxins included in the composition included *C. difficile* toxin A, *C. Difficile* toxin B, both *C. difficile* toxins A and B, or a fragment or derivative thereof. Thomas, Jr. et al disclose that the *C. difficile* toxins contain the repeats which make up the carbohydrate binding domain of toxin A (ARU) or derivatives thereof. Thomas, Jr. et al disclose that the toxins may be recombinant, synthetic or part of a fusion protein which includes a *Helicobactor pylori* urease or polypeptide which facilitates purification of the fusion protein covalently conjugated to an antigen, chemically cross-linked to an antigen or toxoided (i.e. rendered less toxic) (column 3). Thomas, Jr. et al disclose that intranasal administration of antigens give rise to mucosal immune responses in the upper respiratory tract, gastrointestinal and genito-urinary tracts (column 4).

Since the Office does not have the facilities for examining and comparing applicant's immunogenic composition comprising *Clostrium difficile* toxin proteins with the immunogenic composition comprising *Clostrium difficile* toxin proteins of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the immunogenic composition of the prior art does not possess the same material structural and functional characteristics of the claimed immunogenic composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

6. Claims 1-19 and 36-39 are rejected under 35 U.S.C. 102(e) as anticipated by Williams (U.S. Patent No. 5,919,665, filed March 16, 1995).

Claims 1-19 and 36-39 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component wherein said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized.

Williams discloses a composition comprising *C. difficile* toxin A with a poly-histidine tract. Williams also discloses a composition comprising *C. difficile* toxin fusion B proteins. Williams discloses that antibodies produced against the one toxin may be used as an effective therapeutic against one or more toxins produced by other members of the genus Clostridium or other toxin producing organisms such as *Bacillus cereus, Staphylococcus aureus, Streptococcus mutans, Acinetobacter caloaceticus, Pseudomonas aeruginosa* and other *Pseudomonas* species. It would be inherent that the therapeutic vaccine of Williams would comprise toxin A and toxin B repeating units or fragments thereof.

Since the Office does not have the facilities for examining and comparing applicant's immunogenic composition comprising *Clostrium difficile* toxin proteins with the immunogenic composition comprising *Clostrium difficile* toxin proteins of the prior art, the burden is on the applicant to show a novel or unobvious difference between the claimed product and the product of the prior art (i.e.,that the immunogenic composition of the prior art does not possess the same material structural and functional

characteristics of the claimed immunogenic composition). See In re Best, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and In re Fitzgerald et al., 205 USPQ 594.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. Claims 20-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over as applied to claims 1-19 and 36-39 Kink et al and further in view of Schneerson et al *(Infection and Immunity, September, 1992, p. 3528-3532).*

Claims 20-24 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component, wherein the said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized, wherein the microorganism is serotype 14 of *Streptococcus pneumoniae*.

Kink et al have been described above.

Kink et al do not teach serotype 14 *Streptococcus pneumoniae*.

Schneerson et al teach a conjugate vaccine composed of serotype 14 *Streptococcus pneumoniae* capsular polysaccharide bound to Pertussis Toxin. Schneerson et al teach that serotype 14 *Streptococcus pneumoniae* is one of the

common types isolated from patients of all ages with infections caused by *Streptococcus pneumoniae*. Schneerson et al teach that serotype 14 *Streptococcus pneumoniae* capsular polysaccharide does not elicit protective levels of antibodies in infants and children and is a less than optimal immunogen of the 23-valent vaccine for adults. Schneerson et al teach that Pertussis toxin is both a virulence factor and protective antigen of *Bordetella pertussis*. Schneerson et al devised a synthetic scheme to prepare a conjugate of serotype 14 *Streptococcus pneumoniae* and Pertussis toxin. Schneerson et al further teach that the serotype 14 *Streptococcus pneumoniae*-Pertussis toxin conjugate elicited antibodies in mice to serotype 14 *Streptococcus pneumoniae* at levels estimated to be protective in humans and elicited neutralizing antibodies to Pertussis toxin (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the serotype 14 *Streptococcus pneumoniae* capsular polysaccharide of Schneerson et al to the immunogenic composition as taught by Kink et al because Schneerson et al teach that 14 *Streptococcus pneumoniae* capsular polysaccharide is a poor immunogen in humans when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article).

8. Claims 25-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kink et al and Schneerson et al as applied to claims 1-24 and 36-39 and further in view of Taylor et al *(Infection and Immunity, September 1993, p. 3678-3687).*

Claims 25-26 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component, wherein the said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized, wherein the microorganism is *Shigella flexneri* Type 2a.

Kink et al and Schneerson et al as combined *supra* do not teach *Shigella flexneri* Type 2a.

Taylor et al teach a conjugate vaccine comprising *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* bound to bacterial toxoids (carrier proteins). Taylor et al teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* administered to mice alone are not immunogenic. Taylor et al further teach that *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugated to a carrier protein injected into mice subcutaneously in saline solutions elicited serum IgG and IgM antibodies with booster responses. When the *Shigella dysenteria* type 1, *Shigella flexneri* type 2a and *Shigella sonnei* conjugate were adsorbed with alum further enhancement of their immunogenicity was observed (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Shigella flexneri* 2a capsular polysaccharides of Taylor et al to the immunogenic composition as taught by Kink et al because Taylor et al teach that *Shigella flexneri* 2a capsular polysaccharides are poor immunogens when

administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity (the entire article).

9. Claims 27-31 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kink et al, Schneerson et al, Taylor et al as applied to claims 1-26 and 36-39 and further in view of Devi et al *(Proc. National Academy of Science, Volume 88, August 1991, p. 7175-7179)*.

Claims 27-31 are drawn to an immunogenic composition comprising a recombinant protein and a polysaccharide component, wherein the said protein is encoded by a gene from a strain of *Clostridium difficile* and said polysaccharide component is isolated from a strain of a pathogenic microorganism or chemically synthesized, wherein the microorganism is *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B.

Kink et al, Schneerson et al and Taylor et al as combined *supra* do not teach *Escherichia coli* K1 or *Neisseria meningitides* serogroup B.

Devi et al teach that the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are identical (poly{(2→8)-α-N-acetylneuaminic acid)} or poly(α2-8NeuNAc) and serve as essential virulence factors and protective antigens for both pathogens. Devi et al teach that attempts have been made to induce protective immunity to *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B have been thwarted because poly(α2-8NeuNAc), alone or complexed to outer membrane proteins induced low transient levels of IgM antibodies (page 7175). Devi et al teach that when

the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B are conjugated to tetanus toxin (a carrier protein) and injected into mice in a saline solution the capsular polysaccharides elicit both poly(α2-8NeuNAc) IgM and IgG antibodies. Devi et al further teach that re-injection elicited booster responses of both isotypes (T-dependent properties) at dosages applicable for clinical use (page 7178).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the capsular polysaccharides of *Escherichia coli* K1 and *Neisseria meningitidis* serogroup B as taught by Devi et al to the immunogenic composition as taught by Kink et al because Devi et al teach that capsular polysaccharides are poor immunogens when administered alone, but conjugating these capsular polysaccharides to tetanus toxin (carrier proteins) enhances their immunogenicity (the entire article).

10. Claims 31-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kink et al, Schneerson et al,Taylor et al, Devi et al and further in view of Fattom et al *(Infection and Immunity, July 1990, 2367-2374).*

Kink et al, Schneerson et al, Taylor et al and Devi et al as combined *supra* do not teach *Staphylococcus aureus* Type 5 or Type 8 capsular polysaccharides.

Fattom et al teach vaccines composed of *Staphylococcus aureus* type 5 and Type 8 capsular polysaccharides conjugated to *Pseudomonas aerginosa* Exotoxin A. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular

polysaccharides are virulence factors and protective antigens for bacteremia caused by *Staphylococcus aureus*. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides when injected into mice alone do not elicit a serum antibody response. Fattom et al teach that when *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are bound to a protein (i.e. *Pseudomonas aerginosa* exotoxin A) to form a conjugate both *Staphylococcus aureus* type 5 and type 8 elicit antibody responses. Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides acquire T-cell dependent properties as shown by their ability to respond to carrier priming and thus stimulate booster responses (see the Abstract).

It would be *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to add the *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides of Fattom et al to the immunogenic composition as taught by Kink et al because Fattom et al teach that *Staphylococcus aureus* type 5 and type 8 capsular polysaccharides are poor immunogens in humans when administered alone, but conjugating these capsular polysaccharides to proteins enhances their immunogenicity both for active immunization and for preparing high-titered antisera in volunteers for passive immunization (page 2368).

***Status of Claims***

11. No claims are allowed.

***Pertinent Prior Art***

12. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure *(U.S. patent No. 5,773,000 published June 30, 1998, WO 9702836, published January 30, 1997 and Robbins et al, The Journal of Infectious Diseases).*

***Conclusion***

13. Any inquiry of the general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (703) 308–0196.

Papers relating to this application may be submitted to Technology Center 1600, Group 1640 by facsimile transmission. The faxing of such papers must conform with the notice published in the Office Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for the Group 1600 is (703) 308-4242.

Any inquiry concerning this communication from the examiner should be directed to Vanessa L. Ford, whose telephone number is (703) 308-4735. The examiner can normally be reached on Monday – Friday from 7:30 AM to 4:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith, can be reached at (703) 308–3909.

Vanessa L. Ford
Biotechnology Patent Examiner
October 3, 2001

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